Lipoprotein glomerulopathy: an exceptional disease in Caucasian people : a French case with Apolipoprotein E Chicago mutation

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INTRODUCTION

Lipoprotein glomerulopathy is a rare disorder characterized by lipoprotein thrombi distending and occluding glomerular capillary lumina and variable degree of mesangial proliferation. It frequently progresses to renal failure. Rare mutations in apolipoprotein E (ApoE) may contribute to its pathogenesis. From then, more than 70 cases have been reported worldwide, essentially in China and Japan. We described a case of lipoprotein glomerulopathy in a French man, the twelfth ever reported from Europe, with a mutation in the ApoE gene.
To enlighten the pathogenesis, we reviewed the literature for every mutation described.

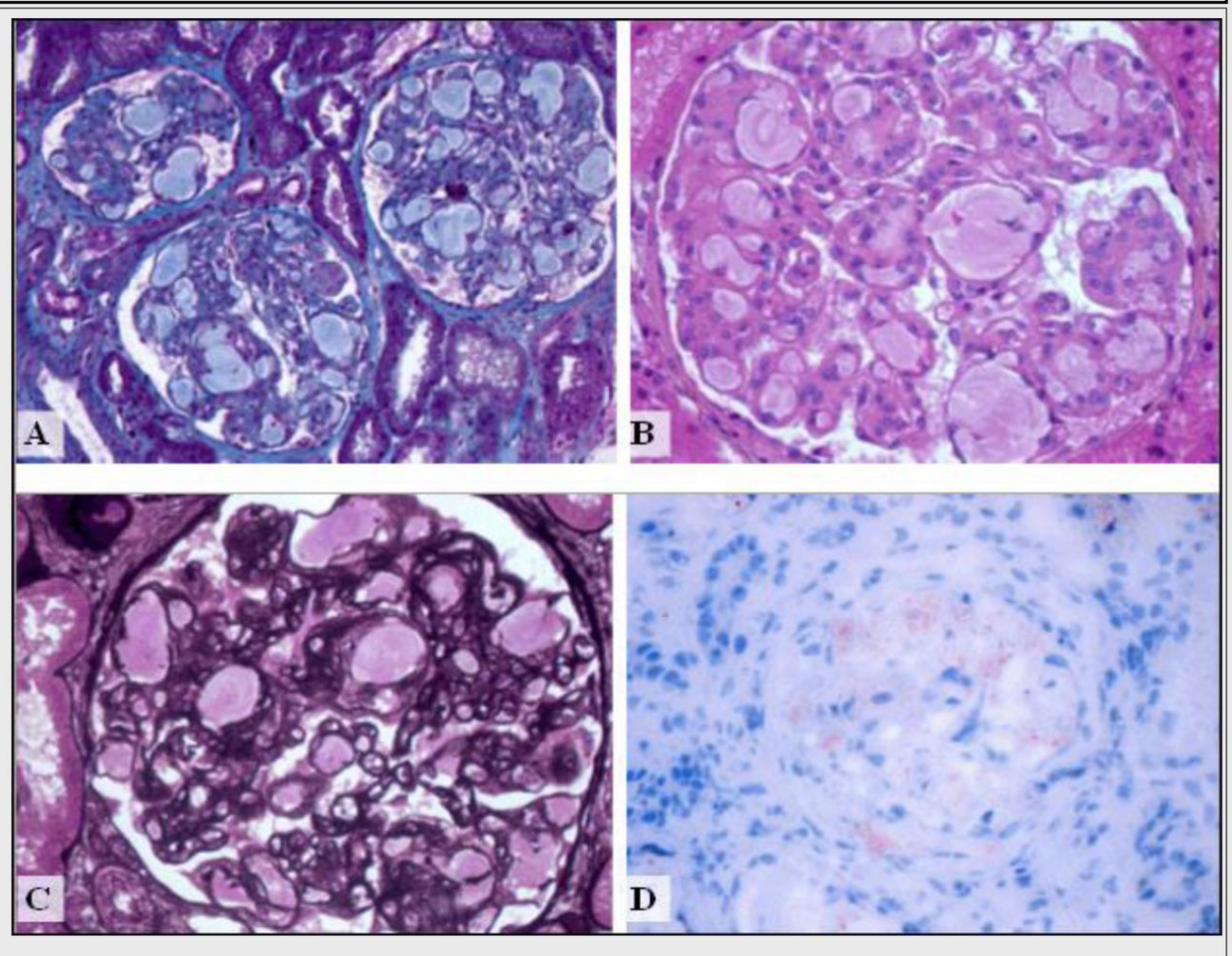
CASE REPORT

A French 40-year-old white man, treated for hypertension, consulted with nephrotic syndrome, with normal renal function. Lipid disorder ressembling type III hyperlipoproteinemia was noticed (hypertriglyceridemia and an overload of VLDL and IDL cholesterol of normal cholesterol-to-triglyceride ratio). ApoE plasma level was high (162 mg/l, normal range from 23 to 63). Phenotyping analysis found an homozygous wild type E3/E3 phenotype.

Histopathology showed lipoprotein glomerulopathy with amorphous thrombi of foamy material in glomerular capillaries. On frozen sections, “Oil Red O” for neutral lipids showed granular staining on the thrombus material, consistent with lipid nature.

DNA sequencing of ApoE found a heterozygous single nucleotide change at position 147, substituting proline for arginine.
This Arg147Pro mutation had been described as ApoE Chicago in 2006.

Lipid-lowering therapy with angiotensin-converting-enzyme inhibitor and weekly LDL apheresis by cascade filtration did not decreased proteinuria.



(A) Trichrome stain (x200). (B) Periodic acid-Schiff stain (x400). (C) Jones silver stain (x400). Almost every capillaries are enlarged and obstructed by amorphous pale stained material. There is a moderate mesangial cell proliferation with some duplication of glomerular basement membrane.

(D) Oil-Red-O stain. The capillary lumina are filled with lipids which appear bright red.

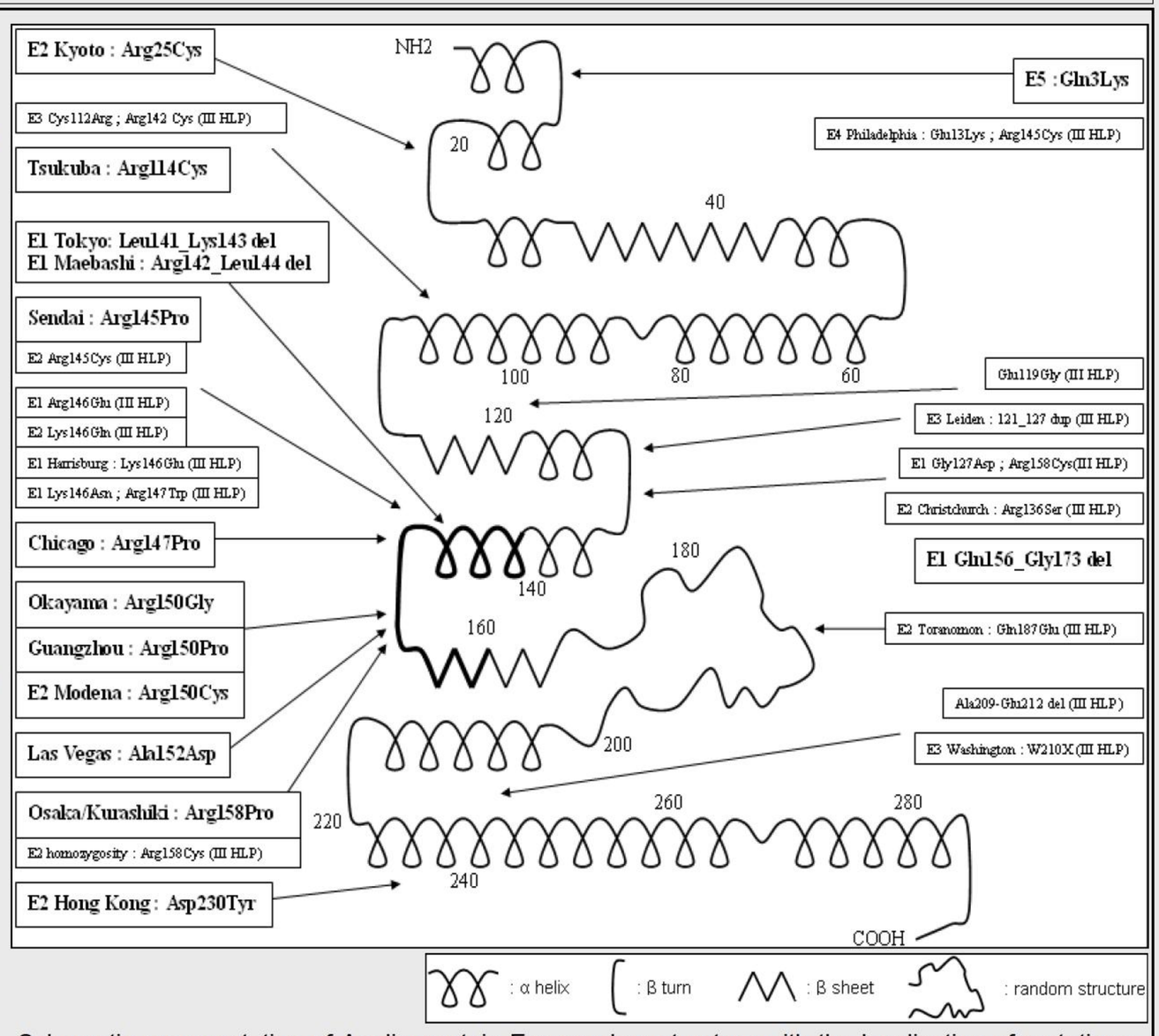
PATHOGENESIS

The pathogenesis of lipoprotein glomerulopathy is uncertain but the contribution of ApoE mutants is clear.

ApoE is an important component of several plasma lipoproteins and has a crucial role in their clearance by interactions with receptors like the LDL-receptor.

Fourteen ApoE mutations leading to lipoprotein glomerulopathy are described in the literature. Other distinct mutations of ApoE are responsible of the dominant form of type III hyperlipoproteinemia.
Nine mutations (among the most frequent) implicate the LDL-receptor binding domain (from residue 136 to 160).

Mutations altering ApoE binding to LDL-receptor or 3D structure of ApoE, lead to low clearance of lipoproteins, that may aggregate and deposit in the glomeruli. After oxidation, these lipids participate in the local injury, with impact on endothelial cells and mesangial proliferation.
Moreover, ApoE produced by mesangial cells plays a crucial role in the regulation of proliferation and survival of mesangial cells and in matrix overproduction.
In lipoprotein glomerulopathy, mesangial proliferation and alteration of glomerular basement membrane could be consequences of ApoE mutations.



Schematic representation of Apolipoprotein E secondary structure with the localisation of mutations described in lipoprotein glomerulopathy (in bold) and type III hyperlipoproteinemia (III HLP). In the molecular structure, the bold line represents the LDL receptor binding site.

CONCLUSION

We reported the second case of lipoprotein glomerulopathy with a variant gene, ApoE Chicago (Arg147Pro) in a French man. Like in most cases, LDL-receptor binding domain was altered.

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